

Reflections on the 'discovery' of the antimalarial *qinghao*

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Artemisinin, *qinghaosu*, was extracted from the traditional Chinese medical drug *qinghao* (the blue-green herb) in the early 1970s. Its 'discovery' can thus be hailed as an achievement of research groups who were paradoxically successful, working as they were at the height of a political mass movement in communist China, known in the West as the Cultural Revolution (1966–1976), a period that was marked by chaos, cruelty and enormous suffering, particularly, but by no means only, among the intelligentsia. On the one hand, China's cultural heritage was seen as a hindrance to progress and Mao set out to destroy it, but on the other hand he praised it as a 'treasure house', full of gems that, if adjusted to the demands of contemporary society, could be used 'for serving the people' (*wei renmin fuwu*). The success of the 'task of combating malaria' (*kang nüe ren wu*), sometimes known as 'task number five hundred and twenty-three', depended crucially on modern scientists who took seriously knowledge that was recorded in a traditional Chinese medical text, *Emergency Prescriptions Kept up one's Sleeve* by the famous physician Ge Hong (284–363).

The 'discovery' of the Chinese medical drug *qinghao* was part of a series of complex historical processes that began with the systematic screening of the Chinese *materia medica* in the late 1960s and led to the first demonstration of the antimalarial effects of an extract of *qinghao* in 1971 [1]. The chemical structure of the active substance in this extract was identified in the late 1970s and was found, totally unexpectedly, to be an sesquiterpene lactone peroxide. Pharmaceutical production of marketable drugs began in 1986. The World Health Organization (WHO) started to investigate artemisinin and its derivatives in the early 1990s and has promoted them on a large scale since 2004. It is difficult now to disentangle the major players [2], all the more so in view of artemisinin's commercial potential and the hoped-for awards of future honours.

Historians and sociologists of science have long deconstructed the notion of 'discovery' and have pointed out the specific social processes that are necessary for producing a 'scientific fact' [3]. They have detailed 'technologies of persuasion' [4] and 'social networks' that make possible the reduplication of experimental results [5] and have highlighted the false

premises of a historiography that celebrates heroic personalities at the expense of recognizing the importance of the social dynamics that lead to the emergence and validation of new findings (for the history of Chinese medicine, see for example [6]). This is said without belittling the ingenuity and dedication to research of individuals such as Professor Tu Youyou at the China Academy of Traditional Chinese Medicine in Beijing and Professor Li Guoqiao at the Guangzhou University of Traditional Chinese Medicine, who have been credited nationally and internationally for their achievements, and other scientists who have worked just as hard but remain unnamed.

Ultimately, I suggest, the unusual political climate and institutional set-up in the People's Republic of China in the 1960s facilitated the modern scientific demonstration of the antimalarial properties of the traditional medicine *qinghao*. At that time, the Chinese government supported Vietnam, then at war with the USA. Because malaria was a prime problem for all armed forces, military research institutions on both sides of the Pacific started to screen substances for their antimalarial properties. The idea of approaching an

institution of traditional Chinese medicine reflected the nationalist fervour of Maoist China. The Academy of Traditional Chinese Medicine employed not only traditional Chinese practitioners but also hard-core scientists (for example chemists, pharmacognosists and pharmacologists), who, like other biomedical doctors, in the 1950s had been forced to attend 'classes of Western medical doctors learning Chinese medicine' (*xiyi xue zhongyi jinxiu ban*) [7]. It was thus a feature specific to institutions of the People's Republic of China that scientists, who themselves had learnt ways of appreciating traditional knowledge, worked side by side with historians of traditional medicine, who had textual learning. This was crucial for the 'discovery' of *qinghao*.

In the late 1960s, when the People's Liberation Army Research Institute sought the help of the China Academy of Traditional Chinese Medicine, the drug of primary choice was Changshan, a drug described in the earliest materia medica, the *Canon of the Divine Husbandman's Materia Medica*, which had been celebrated as an antimalarial in Republican times (1911–1949) [8]. *Qinghao* was among the first 10 items to be screened at the time, but no antimalarial properties were found, because the most active antimalarial substance in the plant extract, artemisinin, is soluble in neither water nor ether. Only 2–3 years later, after various abortive attempts in the laboratory, some brief spells in the field and a variety of projects with several collaborators, did Professor Tu Youyou and her research group develop an extraction method that proved successful.

The breakthrough is now attributed to the finding that a specially prepared ether extract of the traditional drug *qinghao*, when fed to mice infected with malaria, was effective in 95–100% of cases. The earliest official document that reported this success (dated 8 March 1972) explicitly says that this finding built on traditional Chinese medical knowledge: 'From July 1971 onwards, we screened more than one hundred single drugs and composite prescriptions of the Chinese herbal arsenal, and discovered *qinghao* (derived from plant material of the plant *huanghuahao*, i.e. *Artemisia annua*). According to Chinese medicine its main indication is "bone steaming" and "heat vexation", but the Tang, Song, Yuan, and Ming medical records, *materia medica*, and folk knowledge all mentioned its use for treating "malaria" . . . '.

Obviously, the authors of this report did not consider the Chinese medical terms 'bone steaming' (*guzheng*) and 'heat vexation' (*fanre*), which are indications for *qinghao* in the Chinese *materia medica*, to refer to malaria, but only the Chinese medical term

nie, 'intermittent fevers'. The latter was a premodern medical term, which comprised a variety of conditions associated with fever, malaria included, and by the twentieth century it had also become the scientific term for 'malaria'. As indicated in retrospect by Tu Youyou, and also by her colleagues, one sentence in the Chinese medical archive had been central to the development of their technique. It is found in *Emergency Prescriptions Kept up one's Sleeve* by the famous physician Ge Hong (284–363): 'Another recipe: *qinghao*, one bunch, take two *sheng* [2×0.2 l] of water for soaking it, wring it out, take the juice, ingest it in its entirety' [9].

Ge Hong was the first in medical history to recommend the drug *qinghao* for the treatment of 'intermittent fevers' (Figure 1). His recommendation to soak the entire fresh plant in water and to wring it out thereafter (a crucial instruction) probably resulted in an emulsion of water, flavonoids and aromatic oils contained in the stem and leaves (see below). It is possible that this extraction method, which is likely to have yielded artemisinin in larger quantities than any others recorded in the Chinese *materia medica*, was directly linked to its use for acute episodes of fever, with their typically high parasitic load. Both artemisinin and some flavonoids have antimalarial properties and synergism may or may not have played a role [10]. In the future, Ge Hong's recommendation to ingest such a juice wrung out of *qinghao* (rather than a herbal tea or infusion made of hot water poured on to dried plant material) may be crucial for health policies that aim at promoting low-cost preparations of *A. annua* as a herbal antimalarial [11].

Tu Youyou and her colleagues did not use fresh but



Figure 1
Ge Hong

dried plant material. However, as they now stress, they took Ge Hong seriously and applied only low heat during the extraction process. They achieved the most significant effects of the plant extract in a neutral milieu (pH 7.0). This was possible after they had discarded those parts of the herbal extract that made it sour, in December 1971.

Seven months later, in August 1972, another official document reported that 21 patients with malaria had been successfully treated in Beijing with an extract obtained from *qinghao*. Over 90% of them were said to have recovered either from vivax or falciparum malaria. This information was given in one brief sentence among a long list of successful research results of the various groups in the country who were screening Chinese medical drugs for their antimalarial properties.

At the time, *qinghao*'s active substance had not yet been isolated in its pure form, nor was its structure known. When in 1973 Tu Youyou synthesized dihydroartemisinin, to prove that the chemical structure of the active substance had a ketone group, she was unaware that the chemical substance she had produced would later be found to be more effective than the natural compound. Dihydroartemisinin, unlike artemisinin, is water soluble. It is the substance into which artesunate is hydrolysed *in vivo* and clears fever in a short time [12]. Other derivatives of artemisinin were also synthesized in other parts of the country, such as Shanghai and Guangzhou, and pharmaceutical companies in Kunming and Guilin were among the first to bring artemether and artesunate on to the market. A detailed history of the multiple contributions is yet to be written, describing the final identification of the

molecule, the development of the different derivatives and the research that proved its efficacy and made possible its marketing as a drug.

Speculation on the possible role of *qinghao* in contemporary healthcare

What can be learnt for the future from the success story of the scientific 'discovery' of the antimalarial properties of *qinghao*? Although it has taken *qinghao* 33 years to gain full WHO recognition, and although, less than 2 years later in 2006, new policies have banned sole reliance on drugs that contain only artemisinin, its rediscovery is an amazing success for both modern and traditional sciences. Its future may take yet another turn, if Ge Hong's recommendation to drink the raw juice wrung out of a fresh plant proves useful.

In that case, *qinghao*'s importance for the future of medicine may not lie so much in its effectiveness as a modern pharmaceutical but in its potential to revolutionize the organization of antimalarial healthcare in those areas where malaria is endemic and *A. annua* (and *A. apiacea*, see below) can grow in people's backyards. Since the plant is a ruderal that easily grows in wastelands, it has the potential of being grown in a decentralized way among the populations that are most affected (and not only in plantations, as it currently is, for local production of the purified substance artemisinin). Naturally, scientists will first have to determine its precise dosage and optimal formulation as a juice, apart from making *A. annua* (or *A. apiacea*) seeds widely available (Figure 2).

Considering that only three plant species produce artemisinin, namely *A. annua*, *A. apiacea* and *A. lan-*



Figure 2
Artemisia annua

ceolata [10], it is noteworthy that Shen Gua (1031–1095) of the Song dynasty, one of the greatest polymaths in the history of the sciences in China, suggested that it was *A. apiacea* rather than *A. annua* that had striking antimalarial properties (to be sure, he worded this insight differently). He noted in one of his *Dream Pool Essays* of 1086 that there were two kinds of *qinghao*: one had emerald green leaves, which would keep their pine green colour in autumn, while the other's bright green leaves would then grow yellow [13]. Incidentally, this is a feature that modern Chinese botanists also account for in their contrasting descriptions of *A. apiacea* and *A. annua* [14]. Shen Gua furthermore suggested that the kind of plant that the ancients praised (for its antimalarial effects as well as for wound healing and vitality-boosting qualities) was the one that kept its blue-green colour well into autumn [13]. Li Shizhen (1518–1593), who later quoted Shen Gua and others on this issue, decided to give these two different kinds two different names, *qinghao* (the blue-green hao) and *huanghuahao* (the yellow blossom hao) [15]. According to modern botany, they are *A. apiacea* and *A. annua*, respectively (within the limitations intrinsic to any mapping of the modern species concept on to that of traditional Chinese kinds).

The above suggests that Shen Gua, and after him Li Shizhen, valued *A. apiacea* more than *A. annua*. However, modern extraction methods have found higher concentrations of artemisinin in *A. annua* than in any other species. This means that modern science corroborates the botanical distinction of the venerated Shen Gua and Li Shizhen but not their suggestion that *A. apiacea* was the more effective antimalarial. Great scholars can be wrong. Nevertheless, it would be worth testing whether the use of traditional extraction methods from *A. apiacea* produce a mixture of artemisinin, flavonoids and other potentially mildly antimalarial substances more effective than an extract of *A. annua*.

Success stories like that of the rediscovery of *qinghao* are extremely rare, although there is great potential that other pharmaceutically active substances could be extracted from the Chinese *materia medica*. Future rediscoveries of the kind, I argue, will critically depend on whether the institutional set-up and sociopolitical climate encourage natural scientists to speak to specialists of traditional medicines, to respect each other's research and appropriately translate insights from one discipline into the language of the other. They will require full appreciation of all involved and, not least, that the interpretation and translation of ancient, so-called 'superstitious' texts dating from the 'Dark Ages' is as an important intellectual enterprise, as are the

chemical procedures of extraction, isolation and identification of a substance.

For example, Ge Hong's recommendation 'to wring out' the 'fresh' plant is one that not only a modern copy editor of a good scientific journal wanted to delete and a German interpreter mistranslated, but also great physicians like Li Shizhen omitted in their citations. Its message is unusual and does not instantly make sense. Without consulting the original, it would have gone unnoticed; without judicious application of critical, anthropological and historical methods it has been gravely misinterpreted; and without scientific testing its empirical value will remain hypothetical.

Professor Tu Youyou was apparently made aware of Ge Hong's original text and with hindsight she had the ingenuity to translate the recommendation to use 'fresh' (*sheng*) plant material into the language of chemistry in so far as her research group used only low temperatures in the extraction processes, which prevented destruction of the, as we now know, heat-sensitive molecule artemisinin. However, she did not consider the term 'to wring out' very relevant.

The Chinese word that means 'to wring out' (*jiao*) has only recently gained importance as textual specialists have realized that insistence on translating the word may have empirical value [16]. This was possible because during an interdisciplinary workshop a pharmacognosist in the audience remarked that 'wringing out' of the fresh plant may have produced an emulsion conducive to the extraction of artemisinin. The future of this word and, if it proves relevant, the history of *qinghao* in modern healthcare will depend on the force with which medical doctors will pursue this issue, in the recognition that malaria, as any other infectious disease, is primarily a matter of structural violence. Since malaria primarily affects the poor who cannot afford to buy expensive artemisinin combination therapies from the pharmaceutical giants who developed the patent, a perhaps more effective humanitarian aid lies in scientifically investigating the suitability of using a natural plant extract of *qinghao*.

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